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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,386	11/17/2005	Heike Gielen-Haertwig	Le A 36 266	2246

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,386	GIELEN-HAERTWIG ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/9/08*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9-12,14,16,17,19,21 and 22* is/are pending in the application.

4a) Of the above claim(s) *16,19,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,9-12,14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-12, 14, and 17 were rejected in the previous action.

2. Claims 1-4, 6, 9-12, 14, and 17 are pending in this application. Claims 16, 19, 21 and 22 have been withdrawn. Claims 5, 7, 8, 13, 18, 20 and 23-29 have been cancelled. This action is in response to the applicants' amendment after a non-final and reply filed on June 9, 2008.

Withdrawn Rejections/Objections:

3. Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

Claim Objections

4. Claims 1-4 and 14 objected to because of the following informalities: Claims 1-4 and 14 contain non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

5. Claims 1-4, 6, 9-12, 14 and 17 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula (I-A) where R^1 is a hydrogen or an alkyl group; R^2 is a cyano group; R^5 is a methyl group; R^{6A} is a hydrogen, and R^7 is a trifluoromethyl or halogen group, does not reasonably provide enablement for any other compounds or compositions not previously defined by the R variables. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

the compounds and compositions of the invention commensurate in scope with these claims.

6. As applicants and examiner agree, the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors were presented and discussed in the previous action dated March 10, 2008.

In particular, the applicants have provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds of Formula (I-A) where the R variables are other than those previously mentioned above. Applicant has only shown a select number of compounds or compositions within the specification and of these, none of them fall outside of the scope of enablement previously mentioned. Applicants have also provided no guidance as how the compounds are made more active *in vivo*.

"Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush claims must be provided with support in the disclosure for each member of the Markush group*. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is *not sufficient*

to support claims identifying the compound by such composition or formula." See MPEP 608.01(p). There is no guidance or direction to consider disclosures in the art to prepare the diverse compounds and compositions instantly claimed. Applicants bear the responsibility to teach how to make the compounds set forth in their claims.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding the *Wands* factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that applicants are not enabled for making all of these compounds or compositions without undue experimentation. The applicants' arguments are not found persuasive. The rejection is withdrawn in part and maintained in part.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-4, 6, 9-12, 14, and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 and 14 of U.S. Patent Publication Application No. 2008/0021053 in view of *Graver Tank & Mfg. Co. v. The Linde Air Products Co*, (USSC 1950) 339 US 695, 85 USPQ 328.

The applicants arguments revolve around a publication which *inter alia* states, in the controlled experiments performed within the publication a thiourea is more acidic and thus more easily deprotonates than its urea counterpart. The argument that this results in it being nonobvious as a potential invention is not found persuasive.

Applicants argue that one of ordinary skill in the art would not have been motivated to synthesize the same compounds with a C=S in place of a C=O without potentially arriving at a completely different product. Yet the applicants have done just that. Applicants have filed an application for the urea moiety of the thiourea invention in the current application. Ironically, it has as identical use, that of a medicament in the treatment of chronic obstructive pulmonary diseases, acute coronary syndrome, acute myocardial infarction and heart failure development. In addition, the applicants synthesize the final product compounds in an identical fashion, with the reagents differing only in the urea/thiourea starting material.

Applicants argue that the biological activity may differ (the acidity of the thiourea versus the urea) and thus it would not have been obvious to try. However from a chemical standpoint, a compound or composition differing only in a thiourea or urea moiety are similar compounds. This can be seen in the prior art, for example, see U.S. Patent No. 7,074,933. The court decision of *Graver Tank* teaches that the important factor in determining a test for equivalency in a prior art document is whether a person who is reasonably skilled in the art would recognize the equivalency in the compound or composition. In *Ex parte Wiseman* (POBA 1953) 98 USPQ 277, a difluorinated compound was held unpatentable over the prior art dichloro compound on the basis of analogical reasoning. A compound need not be an adjacent homolog or position isomer of a prior art compound in order to be susceptible to a rejection based on structural obviousness; the name used to designate the structural relationship between compounds is not controlling, it is the closeness of that relationship. In *re Payne et al.*

(CCPA 1979) 606 F2d 303, 203 USPQ 245. When chemical compounds have "very close" structural similarities and similar utilities, without more, a *prima face* case of obviousness may be made. *In re Grabiak* (CAFC 1985) 769 F2d 729, 226 USPQ 870.

Relating the information from *Graver Tank* to the current 2008/0021503 publication, it would have been obvious for a person of ordinary skill in the art to attempt to synthesize the urea in the 2-position of the pyrimidine to form a cyclic urea in the same manner that the cyclic thiourea has been synthesized in the current application. The use for these compounds and compositions as medicaments is identical, and the residue groups of the prior art and the application are so similar that one skilled in the art would expect that any differences would be inconsequential in the final product. The difference between sulfur and oxygen are well known in the chemical arts to have similar properties. For example, both elements fall within the same family in the periodic table of the chemical elements. As atoms, both oxygen and sulfur contain the same valence number, similar chemical properties and numerous chemical literature has suggested the attempted use of a thiol over an alcohol or a thiourea in place of a urea and vice versa. Due to the numerous chemical property similarities of oxygen and sulfur, this substitution would be attempted by anyone skilled in the art.

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to synthesize the same compounds or compositions with a pyramid-2-thione instead of a pyrimidin-2-one. The patent publication shows a pyrimidin-2-one and *Graver Tank* shows that a C(=O) group is equivalent to a C(=S) group and that any of these derivatives would be chemical equivalents, and thus would not alter or affect

the claimed compounds in any significant way. Due to the numerous chemical property similarities of sulfur and oxygen, this substitution would be attempted by anyone skilled in the art who was attempting to make pyrimidin-2-thiones. The claims above are obvious because the substitution of one known element for another (sulfur for oxygen) would have yielded predictable results in the process to one of ordinary skill in the art at the time of the invention. The applicants' arguments are not found persuasive and the rejection is maintained.

Conclusion

9. Claims 1-4, 6, 9-12, 14, and 17 are rejected.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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